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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,500	11/29/2000	David A Cheresch	TSRI 651.1	5356

2387 7590 12/11/2003

OLSON & HIERL, LTD.
20 NORTH WACKER DRIVE
36TH FLOOR
CHICAGO, IL 60606

EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 12/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/701,500

Applicant(s)

CHERESH ET AL.

Examiner

Richard Schnizer, Ph. D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 22 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-4,12-16,33 and 34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-4,12-16,33 and 34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

An amendment was received and entered on 9/22/03. Applicant's election without traverse of Group III, claims 1-4, 12-16, 33, and 34 is acknowledged.

Claims 5-11, 17-32, and 35-38 were canceled as requested.

Claims 1-4, 12-16, 33, and 34 are pending and under consideration in this Office Action.

Claim Objections

Claims 12 and 13 are objected to because they fail to further limit claim 1. These claims are drawn to the article of manufacture of claim 1 "wherein said administering comprises" various routes of administration (claim 12) or a single does intravenously (claim 13). As noted below under 35 USC 112, second paragraph rejections, there is no antecedent basis for the "said administering" clauses in these claims. As a result these clauses lack meaning, and the claims fail to further limit claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 1-4 and 12-16 are indefinite because it is unclear what are the metes and bounds of "a tissue associated with a disease condition". More particularly it is unclear what type of association is required, and it is unclear what are the metes and bounds of a disease condition. Nearly every tissue can be associated with some disease condition or other, however, it is unclear as to whether the tissue in which the effect is desired must be diseased or must merely be capable of becoming diseased. Also it is unclear whether the claims refer to tissues that are associated e.g. by physical location, or alternatively by function.

Claims 12 and 13 are indefinite because they recite "said administering" without antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising a nucleic acid encoding an active src protein that can be used to potentiate angiogenesis in a tissue at a site at which the active src protein has been directly administered, does not reasonably provide enablement for an oligonucleotide encoding an active src protein, a nucleic acid encoding an active src protein that inhibits angiogenesis, or that can be used to treat diseases generally, or that can be used to stimulate angiogenesis at sites other than that to which it is directly administered. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are directed to a composition with an intended use, and this rejection addresses the scope of enablement of the claimed composition for that intended use. The claimed composition is intended to be used to treat disease conditions by modulating angiogenesis. The claims do not limit the nature of the disease conditions that may be treated, nor the result of the treatment. Therefore the scope of the intended use includes treatment of any disease condition, and the extent to which the disease is treated embraces complete cure. This includes disease conditions that are unrelated to angiogenesis such as cystic fibrosis or muscular dystrophy. None of the claims addresses the relationship between the site of administration and the site of modulation of angiogenesis. Only claim 2 requires that the modulation of angiogenesis must be a positive modulation, i.e. a potentiation rather than an inhibition. Because the claims are limited to nucleic acids encoding an "active Src protein", the scope of the claims embracing inhibition of angiogenesis cannot be enabled, particularly in view of the specification at page 8, lines 10-29 which defines active src proteins as those that potentiate angiogenesis, and inactive Src proteins as those that inhibit angiogenesis.

It is also noted that the claims are directed to "an oligonucleotide having a nucleotide sequence capable of expressing an active Src protein." The specification provides no definition of the term "oligonucleotide", however the Merriam Webster's Collegiate dictionary, and the Steadmans Medical Dictionary, each define an oligonucleotide as a chain of nucleotides of up to 20 nucleotides in length. Src proteins

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generally comprise over 500 amino acids, and would thus require about 1500 nucleotides to encode a full length protein. The active site alone of Src is about 60 amino acids (See e.g. Chan et al (J. Biol. Chem. 271(37): 22619-22623, 1996, Fig. 1 on page 22620). Clearly an oligonucleotide, as defined in the art, is not capable of encoding an active src protein, and one of skill in the art could not make an oligonucleotide having a nucleotide sequence capable of expressing an active Src protein.

With regard to the treatment of diseases in general through the delivery of nucleic acids, at the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist

including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Reviews/Genetics 1: 9199, 11/2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

While these shortcomings illustrate the unpredictability of treating diseases in general through gene therapeutics, and of obtaining complete cures to diseases, they are also particularly relevant in view of the intended use of the claimed composition to elicit a therapeutic effect at a target site by administration of a gene therapeutic to a site other than the target site. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review,

which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1).

Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification teaches a working example of potentiation of angiogenesis in chick chorioallantoic membranes by direct administration of a retroviral expression

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vector encoding Src A. The art teaches numerous examples of methods of inducing angiogenesis at a defined site by direct administration to the site of nucleic acids encoding various angiogenic factors such as vascular endothelial growth factor (VEGF). See e.g. US Patents 5,652,225 and 6,121,246 to Isner (prior art), and US Patent 6,329,348, to Crystal (post-filing art). The prior art also taught that active src polypeptides such as pp60c-src and v-src increase VEGF expression and activity, and were suspected of promoting angiogenesis. See e.g. Mukhopadhyay et al (Nature 375 (6532): 577-581, 1995, abstract) or Mukhopadhyay et al (Cancer Research 55: 6161-6165, 1995, abstract). Thus the prior art at the time of the invention supports methods of promoting angiogenesis at specific sites to which nucleic acids encoding angiogenic factors have been directly administered, but does not support the treatment of diseases generally by administration of nucleic acids encoding active src proteins.

The specification provides no guidance as to how one can affect any disease other than those directly affected by angiogenesis, and provides no guidance as to how one can achieve delivery and expression of angiogenic expression constructs sufficient to cause therapeutic angiogenesis at sites distal to the site of administration. In view of the state of the art at the time of the invention, particularly the difficulties in vector targeting, gene delivery, and gene expression, one of skill in the art would have to perform undue experimentation to use the claimed compositions to treat disease in general, or to cause angiogenesis at target sites other than the site of administration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 12-14, 16, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Zang et al (J. Biol. Chem. 272(20): 13275-13280, 1997).

Zang teaches compositions comprising plasmid expression vectors encoding c-Src mutants comprising a Y527F mutation (i.e. Src A). The compositions may comprise liposomes. See paragraph bridging pages 13275 and 13276.

Claims 1-4, 12, 15, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Dent et al (Biochem. J. 303: 105-112, 1994).

Dent teaches a composition comprising a viral expression vector encoding c-Src mutants comprising a Y527F mutation (i.e. Src A). See paragraph bridging columns 1 and 2 on page 106.

One might argue that the claimed compositions distinguish over Zang and Dent because they comprise packaging material and a label reciting an intended use. However, it is well settled that the application of particular printed matter to an old article cannot render the article patentable. In re Thomas J. Dixon, 18 C.C.P.A. (Patents) 711, 44 F.2d 881, 7 USPQ 209 ; In re Robert C. Russell, 18 C.C.P.A. (Patents) 1184, 48

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F.2d 668, 9 USPQ 181 ; In re Reeves, 20 C.C.P.A. (Patents) 767, 62 F.2d 199, 16 USPQ 110 ; In re McKee, 20 C.C.P.A. (Patents) 1018, 64 F.2d 379, 17 USPQ 293 ; In re Hansen, 33 C.C.P.A. (Patents) 979, 154 F.2d 684, 69 USPQ 332 . Accordingly, the mere labeling of an old composition as a product capable of a new use does not make it a new or different composition within the meaning of the patent statutes. The rejected claims represent an attempt to patent an old product on the basis of a statement that it is intended for a new use. Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned. Thus, Zang and Dent anticipate the claims.

Conclusion

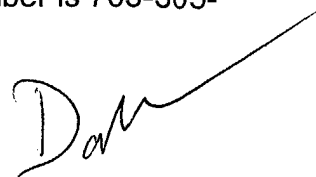
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should

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be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.

A handwritten signature in black ink, appearing to read 'David', with a long, sweeping horizontal line extending to the right.

DAVID NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.